Primary Cilium-Autophagy-Nrf2 (PAN) Axis Activation Commits Human Embryonic Stem Cells to a Neuroectoderm Fate.

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Authors: Jiwon Jang, Yidi Wang, Matthew A Lalli, Elmer Guzman, Sirie E Godshalk, Hongjun Zhou, Kenneth S Kosik

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Public Summary:
Human embryonic stem cells (hESCs) can be directed toward a variety of different cell fates. The first decision to be made is whether or not to become mesendoderm (ME) or neuroectoderm (NE). In this study, we describe the molecular pathway that leads cells to become NE. Coupled with lineage-specific lengthening of the cell division cycle, we show that the cells change their production of cilia, a sall protrusion from the cell. This in turn stimulated the autophagy pathway, whereby internal cellular components are recycled. Furthermore we found changes in specific transcription factors. Thus, we have identified a primary control axis coupled to cell-cycle progression that directs hESCs toward NE.

Scientific Abstract:
Under defined differentiation conditions, human embryonic stem cells (hESCs) can be directed toward a mesendoderm (ME) or neuroectoderm (NE) fate, the first decision during hESC differentiation. Coupled with lineage-specific G1 lengthening, a divergent ciliation pattern emerged within the first 24 hr of induced lineage specification, and these changes heralded a neuroectoderm decision before any neural precursor markers were expressed. By day 2, increased ciliation in NE precursors induced autophagy that resulted in the inactivation of Nrf2 and thereby relieved transcriptional activation of OCT4 and NANOG. Nrf2 binds directly to upstream regions of these pluripotency genes to promote their expression and repress NE derivation. Nrf2 suppression was sufficient to rescue poorly neurogenic iPSC lines. Only after these events had been initiated did neural precursor markers get expressed at day 4. Thus, we have identified a primary cilium-autophagy-Nrf2 (PAN) control axis coupled to cell-cycle progression that directs hESCs toward NE.